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The association between quality of asthma treatment and asthma exacerbation in Korea

– A national population - based study –

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Abstract

The association between quality of asthma treatment and asthma exacerbation in Korea

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Background/Objective: Health Insurance Review & Assessment service(HIRA) has evaluated the effect of medical care on asthma and its cost for each medical institution since 2013. However, the validity of evaluation results by HIRA has not been carefully examined. The main goal in my thesis is to test whether the asthma evaluation is significantly associated with asthma care by using the claim data received from HIRA.

Method: The claim data from 1 July 2013 to 30 June 2016 were requested to HIRA. Data generated by HIRA were denoted by M20170512670 and it was remotely accessed for statistical analyses. I considered subjects with J45(asthma) or J46(status asthmaticus) diagnosis code and who aged 15 years or older. T20(general information), T30(healthcare service provided) and T53(outpatient prescription) from M20170512670 were used to determine asthma medication and asthma patients, and then the asthma exacerbation medicines were determined and their rank sums of asthma medicines were calculated. Evaluation results of asthma care for each medical institution were regressed on the asthma exacerbation rate.

Results: I evaluated the association between evaluation results by HIRA and asthma exacerbation rate for each medical institution with regression. If evaluation of medical institution by HIRA was appropriately conducted, medical institution with good evaluation may have smaller asthma exacerbation rate due to low asthma

hospitalization and asthma exacerbation drug use than other medical institutions. However, the asthma exacerbation rate and the medical institution with good evaluation were not significantly associated. Furthermore, the asthma exacerbation rate due to the use of asthma exacerbation drugs has been consistently decreasing, and medical institution with good evaluation tends to have higher asthma hospitalization.

Conclusion: Results suggests that evaluation by HIRA may improve the quality of asthma treatment in medical institutions but it does not successfully assess effectiveness of asthma treatment. The results in my thesis may provide useful information to improve the project of HIRA for evaluation on asthma care and further investigation on evaluation criteria for asthma care is necessary to improve the quality of asthma treatment.

Keyword : Asthma, Exacerbation, Quality of asthma treatment, Evaluation of appropriateness, Korea
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1. Introduction

Asthma is a heterogeneous disorder characterized by chronic airway inflammation. It is characterized by symptoms such as wheeze, shortness of breath, chest tightness and cough, together with variable expiratory airflow limitations(GINA guideline 2017). Asthma is a major chronic disease that affects about 300 million people worldwide. Acute exacerbations can be life-threatening, and chronic diseases can cause disruption to daily life. The prevalence of asthma continues in Korea to increase, suggesting the possibility that asthma will soon become a socioeconomic burden in Korea, which is rapidly entering an aging society.

Asthma is also a disease that requires many medical resources. According to the medical statistics index by Health Insurance(2015), the number of patients is 1.66 million (3.55% of the total number of medical patients), and the medical expenses are 263.5 billion won (0.47% of total medical expenses). It occupies 6th place in the 10th chronic disease burden(Yoon, 2009). Asthma is a typical ambulatory care sensitive condition (ACSC) that can prevent the exacerbation and hospitalization of patients when they are adequately treated, and the cost of medical care can be substantially reduced if patients are properly managed by the medical institutions.

The Health Insurance Review & Assessment service(HIRA) has evaluated the medical behavior of medical institutions since the second half of 2001 through the amendment of the National Health Insurance Act 2000. Asthma has been included in the target disease to evaluate the adequacy of medical behavior by medical institution by HIRA since 2013. As a result of the evaluation of the medical institution' s medical behavior in 2015, the rate of 'Pulmonary function test' which is an evaluation indicator of HIRA increased by 1.41% from 23.47% to 24.88% compared to 2014, and the rate of 'patients who visited continuously' increased by 0.68% from 71.20% to 71.88%. However, it is only a small increase, so it is necessary

to compare the effectiveness of the HIRA project. The rate of pulmonary function tests required for asthma diagnosis was 81.61% for tertiary general hospitals, 61.30% for general hospitals, and 18.06% for clinics. When comparing these figures, there was a big difference between hospitals. The proportion of ICS prescriptions was 87.14% for tertiary general hospitals, 65.18% for general hospitals, and 17.80% for clinics. This number also shows the differences between hospitals, so it is necessary to verify whether the HIRA project is effective.

Currently, no studies have evaluated the appropriateness of the HIRA's project on asthma care scientifically, and it is necessary to analyze scientifically how the HIRA project affects the quality of asthma treatment.

2. Theoretical Background

2.1. Asthma treatment guideline

The prevalence of asthma among Korea adults has increased from 4,944 to 5,707 cases per 100,000 population (from 3760 to 4445 in men and from 6108 to 6951 in women) (S. Kim et al., 2013) from 2006 to 2010, and the prevalence of asthma, which is expected to increase to around 400 million worldwide by 2025 (Masoli, Fabian, Holt, & Beasley, 2004). In 2016, the number of asthma patients in Korea was 1.97 million (4.16% of the total number of medical personnel) and total medical expenses of 213 billion won (0.34% of total medical expenses). Asthma requires a large amount of medical resources. The prevalence of preventable asthma in Korea is about 94.5 per 100,000 people by 2015, more than twice the average of 46.7 in OECD countries (OECD, 2017).

Patients with asthma have similar clinical features but their pathologies are very heterogeneous. Asthma can be classified by demographic, clinical, and pathophysiological criteria. Many phenotypes have been identified as allergic asthma, non-allergic asthma, late-onset asthma, asthma with fixed airflow limitation, asthma with obesity (Korean guideline for asthma, 2015).

As the prevalence of asthma has increased and the socio-economic importance of the disease has been recognized, the international guidelines for the diagnosis and treatment of asthma were first established and published in 1992 in order to convey the consensus of experts on the treatment of asthma. The "Korean Academy of Asthma, Allergy and Clinical immunology" published the first guidelines for asthma treatment in Korea in 1994, and revised the guideline in 2015. The Guideline covers both adult asthma and pediatric asthma, and is based on the Global Initiative for Asthma (GINA) 's Global Strategy for Asthma Management and Prevention, British Guideline on the Management of Asthma. This is the latest edition of the Korean guideline for Asthma.

Currently, asthma is treated with Inhaled Corticosteroids(ICS) and leukotriene receptor antagonist (LTRA), and in the case of more severe asthma, the maintenance regimen is gradually strengthened by adding a sustained β2-agonist (LABA) (GINA 2016, NAEPP 2007). Since it is known that ICS relieves systemic side effects and develops strong local effects, ICS is recommended as a primary therapeutic agent in clinical practice guideline (Korean guideline for asthma, 2015). Nonetheless, the prescription rate of ICS is low in Korea, and when we look at the distribution of prescription drug formulations used for asthma patients, 83.4% of the oral formulas and ICS were only 16%(Jang, Kim, Sohn, Park, & Kim, 2014). The reason why the use of ICS is low is that Korean physicians often depend on oral medications rather than ICS (Lee, 2004). The reasons for low ICS use include the stereotypes that oral drugs are effective, the difficulty and resistance of inhaler manipulation, the fear of side effects of ICS, the underestimation of chronic airway disease, the cost of relatively expensive ICS. It seems that the compliance rate of the guidelines for recommending prescription for ICS is low due to unfamiliarity with the guidelines for airway disease treatment or the lack of knowledge of ICS education methods (Cho et al., 2006). In addition, the negative memories of past insurance systems, when insurance was cut when prescribing inhalants in primary medical institutions, may have influenced Korean physicians' treatment patterns. Analysis of national health insurance data from 2003 to 2010 in Korea to evaluate Korean physicians' use of ICS showed that the prevalence rates of ICS before and after the distribution of guideline were 13.3% and 16.4%, respectively. However, the effect of guideline was not significant. ICS prescriptions at hospitals and general hospitals were significantly increased, but there was no significant change in primary clinics, which covered 81.7% of asthma cases. From the in-depth interview, we could identify that the reimbursement criteria of HIRA and patient’s preference for oral drug were barriers for the ICS prescription (S. H. Kim et al., 2015).

However, the use of ICSs is the cornerstone of asthma treatment. A retrospective cohort study using the Health Improvement Network general practice database (THIN, United Kingdom) and Cegedim Longitudinal Patient Data (France) showed that patients with asthma using systemic steroids or antibiotics were less likely to use ICS. Patients with fewer ICS use visited the hospital more often, and asthma was not well controlled. In addition, the greater the use of ICS, the lower the risk associated with the use of systemic steroids (Laforest et al., 2015) Failure to follow the asthma guidelines may result in poor quality of life, disproportionate use of medical resources, and side effects of systemic steroids administered on a regular basis. ICS is known to be effective not only in clinical efficacy but also in cost reduction of asthma treatment. According to a study of Medicaid subscribers in the state of North Carolina in the US, ICS-treated patients showed a 23.7% reduction in total cost compared to controls without any steroids such as oral or inhaled medication(J. Kim, Lee, Kim, & Lee, 2008). Given the fact that the usual use of ICS to control asthma is more cost-effective, it is expected that the social costs of asthma will increase if the asthma care guidelines are not followed at the medical institutions. Social costs, including direct and indirect costs incurred from asthma in Korea, were considerable at $ 4.1 billion as 0.44% of GDP in 2004(CY. Kim et al., 2011). Considering that asthma morbidity and mortality are increasing every year, the social cost of asthma is expected to increase further in the future.

Therefore, it is necessary to confirm whether the project of the HIRA will induce compliance with the guideline of medical institutions to improve the quality of asthma treatment and to contribute to the appropriation of medical expenses.

2.2. Foreign status on quality evaluation of asthma care in hospital

Since the healthcare sector has a direct impact on the health and life of the people, more government regulation is needed than in other areas. It is difficult to guarantee the quality of patient safety and quality of care, because of the rapid change in its environment, such as the complexity, the plurality of stakeholders, the emergence of new diseases and the development of medical technology. There are various medical institutions for regulating the healthcare sector. In addition, the regulatory system can be divided broadly into voluntarism, market mechanism, self-regulation, meta-regulation, and direct and command(Healy & Braithwaite, 2006).

In the meantime, a great deal of medical care has relied on self-regulation of medical institutions, such as observing the mortality rate of patients in hospitals or confirming treatment outcomes. However, there is a limit. In many countries, various regulations have been introduced to regulate the healthcare sector, and a new management system has been introduced in areas that were managed by self-regulation for the quality control of medical care, including patient safety law(Downie et al., 2006). Government and evaluation bodies of the United States and the United Kingdom have released evaluation results since 1990. In the Centers for Medicare & Medicaid Services(CMS), Pennsylvania Healthcare Cost Containment Council(PHC4), Leapfrog in the United States and National Health Service(NHS) in the United Kingdom have published the results of the evaluation along with information on the amount of medical care and medical expenses. In addition, quality improvement programs are developed and provided to medical institutions in various ways such as Quality Improvement Organizations (QIO) and Institute for Healthcare Improvement (IHI) in the United States. In order to verify that medical institutions provide good quality medical services to patients, the quality of

medical services such as the medical service process, treatment outcome, patient perception, organizational structure, and system are evaluated.

In the United States, many institutions are involved in assessing quality of medical care. The National Quality Forum (NQF) reviews and supports evaluation indicators proposed by organizations such as the American Medical Association (AMA) or the Agency for Healthcare Research and Quality (AHRQ). Physician Consortium for Performance Improvement (PCPI) of AMA conducts a quality assessment of asthma patient care through a variety of indicators. And the National Committee for Quality Assurance (NCQA) is the main body performing authentication based on the evaluation results. NCQA also publishes reports on quality measurements using Healthcare Effectiveness Data and Information Set (HEDIS). Medicare and Medicade Services (CMS) use measures approved by the NQF, and NCQA establishes and applies reimbursement and incentive payment criteria. The evaluation indicators of PCPI are shown in the Table 1. As shown in Table 1, not only the asthma medications use of the GINA guideline but also indicators such as emergency room visits or hospitalization due to asthma exacerbation were selected as evaluation indicators in PCPI. This means that not only the compliance with the guidelines of medical institutions was assessed but also the evaluation of asthma exacerbation as a result of medical treatment. The evaluation indicators of HIRA project only reflect the compliance of the medical institution with the use of asthma medications in ‘Korean guideline for asthma(2014)’. This fact can be a rationale that the variables of asthma exacerbation and hospitalization set in this study is appropriate to assess the evaluation indicators of HIRA.

In United Kingdom, National health Service(NHS) has introduced the Quality and Outcome Framework (QOF) since 2004, which is the world's largest incentive compensation system that measures the clinical and organizational quality of primary care. As the first

QOF indicator (2004) was introduced without preliminary validation, National Institute for Health and Clinical Excellence (NICE) has improved clinical quality measures in line with international guidelines and has been determined by negotiating which indicators to include with the General Practitioners Committee. The QOF is a project of pay for performance(PIP) for general practitioner, combining a number of goals to create a composite indicator of a total of 1,000 points. These indicators include 142 indicators in four categories of clinical, organizational, patient experience, and value-added services. Nearly all general practitioners participate in the QOF, and the amount covered by the QOF represents an average of 20% of the general revenue(H. J. Yoon & Park, 2017). Stephen M Campbell attempted this indicators of QOF to verify the validity of the quality measure index(Campbell et al., 2011). A study of the effectiveness of QOF performed by Steel et al suggests that the quality of care improves progressively but that the rate of improvement is small when compared to trends before the introduction of QOF(Steel, Nicholas, Willems, & Sara, 2010).

In Germany, the Disease Management Program (DMP), which was introduced in 2006, will improve the quality of asthma care and reduce costs. Traditionally, in Germany, sickness funds have been automatically decided according to occupation, but the difference between subscriber income level, risk structure, and insurance rate has been large. In addition, the sickness fund has paid attention to the average medical cost of patients with chronic illnesses, not the actual costs, so some patients with chronic disease are interested in DMP, which has improved medical quality and cost effectiveness. When the patient is managed within the DMP, the medical institution receives additional costs. All DMPs are qualitatively certified by the Federal Social-Insurance Authority (Bundesversicherungsamt). DMP is open to all patients and providers, but once contracted with it, they must follow the rules and receive the same guidelines, if the patient status is the same regardless of the sickness fund (Busse, 2004). The guidelines of the DMP are established by experts from

universities, medical associations, etc., with the participation of stakeholders based on the essentials. Approximately 70% of general practitioner are participating in the DMP although the participation rate is different for each disease deposit (H. J. Yoon & Park, 2017).

In case of Taiwan, the Quality-based Payment Initiatives (QBPI) or Pay-by-Performance (P4P) system was introduced in November 2001. QBPI is an incentive to pay additional rewards as a form of reimbursement if medical institutions develop and improve their care procedures. QBPI is reimbursed by outcome according to disease management model in pneumonia, diabetes, asthma, cervical cancer examination result and breast cancer treatment area. In the case of asthma, an evaluation indicator similar to that of the HIRA, such as the rate of medical service utilization (number of visits per patient) and the rate of following up patients within the half-year, is established.

Table 1. Evaluation criteria of asthma care in foreign countries

Country	Program	Indicators
US	PCPI of NCQA	▪ Pharmacologic Therapy for Persistent Asthma–Ambulatory Care Setting. : Percentage of patients aged 5 y and older with a diagnosis of persistent asthma who were prescribed long-term control medication.This measure will be calculated with 3 performance rates: 1. Patients prescribed inhaled corticosteroids (ICS) as their long-term control medication. 2. Patients prescribed alternative long-term control medications (non-ICS). 3. Total patients prescribed long-term control medication. ▪ Assessment of Asthma Control : Percentage of patients aged 5 y and older with a diagnosis of asthma who were evaluated for asthma control (comprising asthma impairment and asthma risk) at least once during the measurement period. ▪ Tobacco Smoke Exposure: Screening : Percentage of patients aged 5 y and older with a diagnosis of asthma (or their primary caregiver) who were queried about tobacco smoke exposure at least once

		during the measurement period. ▪ Tobacco Smoke Exposure: Intervention : Percentage of patients aged 5 y and older with a diagnosis of asthma who are exposed to tobacco smoke (or their primary caregiver) who received tobacco use cessation intervention at least once during the measurement period. ▪ Assessment of Asthma Risk : Percentage of patients aged 5 y and older with an emergency department visit or an inpatient admission for an asthma exacerbation who were evaluated for asthma risk. ▪ Asthma Discharge Plan : Percentage of patients aged 5 y and older with an emergency department visit or an inpatient admission for an asthma exacerbation who are discharged from the emergency department OR inpatient setting with an asthma discharge plan. ▪ Asthma Action Plan : Percentage of patients aged 5 y and older with a diagnosis of asthma who received a written asthma action plan at one or more visits during the measurement period.
UK	QOF	▪ Establish and maintain a register of patients with asthma, excluding patients with asthma who have been prescribed no asthma-related drugs in the preceding 12 months. ▪ Percentage of patients aged 8 or over with asthma (diagnosed on or after 1 April 2006), on the register, with measures of variability or reversibility recorded between 3 months before or anytime after diagnosis (thresholds 45-80%). ▪ Percentage of patients with asthma, on the register, who have had an asthma review in the preceding 12 months that includes an assessment of asthma control using the 3 Royal College of Physicians(RCP) questions (thresholds 45-70%). ▪ Percentage of patients with asthma aged 14 or over and who have not attained the age of 20, on the register, in whom there is a record of smoking status in the preceding 12 months (thresholds 45-80%).
Germany	DMP	▪ Percentage of registered asthma patients being properly managed ▪ Percentage of asthmatic patients who completed the training (among the patients recommended for training) ▪ Percentage of patients using self-management plans ▪ Percentage of patients who visited the emergency room during the past 12 months ▪ Percentage of patients regularly using inhaled steroids (among regular medication patients)

		▪ Percentage of patients who have been assessed for inhalant use technology (among patients using inhalants)
Taiwan	QBPI, P4P	▪ Medical service utilization(number of visits per patient) ▪ Following up patient rate within the semester ▪ Average rate of emergency room visits per patient ▪ Average number of hospitalizations per patient

2.3. Korean status on quality evaluation of asthma care in hospital

In Korea, the National Health Insurance Act revised in July 2000 introduced the appropriateness of medical care and defined it as the work of HIRA. Therefore, HIRA evaluated whether the medical behavior of medical institutions was appropriate in terms of medical aspects and cost / effectiveness. In the first year of evaluation, the evaluation was started focusing on diseases with a high frequency or cost ratio in the total medical care benefit. The evaluation area was expanded to clinical fields such as acute myocardial infarction, acute stroke, and prophylactic antibiotic use. Recently, the evaluation area has been expanded to severe and chronic diseases according to changes in social environment. The HIRA analyzes and grades the medical institutions through the evaluation of the medical institution' s medical behavior, and this data is provided as reference information for the medical use of the public. The National Health Insurance Service (NHIS) notifies the result of the evaluation to the medical institutions, and it motivates them to improve their own quality of medical treatment. HIRA's evaluation results are shared with the public based on the idea that in response to the surging social needs and interests of medical services, the public should be provided medical services with good quality as a basis of the right information for selecting the medical service. In addition, HIRA's projects are diversifying into the business that medical care cost can be paid by adding or subtracting to patients with some of diseases (acute myocardial infarction, cesarean delivery, acute stroke, surgical prophylactic antibiotics use, outpatient drug appraisal, hemodialysis), incentive business (hypertension, diabetes), and quality improvement support projects

(Hong & Park, 2013).

However, there are arguments to evaluate the performance of the project positively for the projects carried out by HIRA, but there are negative claims pointing out the problems of the project. In order to positively evaluate the business of pay for performance (PFP) by HIRA, which has been in force since 2007, it is argued that it should expand the diseases area to appraisal and expand the institutions covered by the business of PFP. However, there is a criticism that the evaluation of appropriateness of medical treatment behavior in Korea is limited to the achievement of the evaluation institution like HIRA for the reduction of the medical expenditure of the government. In addition, since the publicly available results of evaluation are the average results of the medical institutions in Korea, they are constantly raising the awareness that there is a limit to apply them as a result common to all medical institutions.(Hong & Park, 2013). PFP system in Korea was narrow in scope and target indicators of quality of medical care, and lack of participation of stakeholders at the time of development of PFP system. In addition, there is a difference from the OECD countries in that the medical provider can not decide whether to participate in PIP or not and the medical institution is evaluated relatively. This limits the achievement of the goal of improving the quality of medical care (H. J. Yoon & Park, 2017).

Since 2013, asthma has been included in the disease to be evaluated for the appropriateness of the asthma treatment behavior of the medical institution. HIRA has assessed medical institutions diagnosed with asthma and accrued for outpatient medical care benefits. And HIRA has assessed the patients using a medical institution who were diagnosed with asthma (J45, J46) during the evaluation period and who were aged 15 or older. The criteria for evaluation of asthma was established on April 23, 2013 through the gathering of expert opinions based on the research and domestic and foreign literature and the review of the central evaluation

committee within HIRA. The central evaluation committee of the HIRA is composed of a large number of specialized physicians, but their opinions are limited in the selection of the evaluation indicators because they are not representative of the opinion of the physicians or the physicians' association, which is the stakeholder of the evaluation project.

Assessment of adequacy of medical institutions for asthma conducted from 2013 has been carried out four times until this year, and evaluation results of the three years up to the third stage until 2016 are as follows (The results of asthma evaluation report by HIRA, 2015). The evaluation results of the HIRA show that the quality of asthma care in Korea is improving, but there is little evaluation as to whether this will lead to asthma hospitalization or reduction in visits to the emergency room. Assessment indicators of the HIRA were evaluated at the medical institution level by dividing the level of compliance of the asthma care guidelines into various factors and could be influenced by confounding factors of personal level such as personal history and seasonality of asthma medications (Yun, 2016). Therefore, it is necessary to use the variable of rank-sum reflecting the individual severity.

Table 2. Summary of evaluation results by HIRA

Evaluation area	Name of indicators	Interpretation of indicators
Test	Pulmonary function test execution proportion	- In all categories of medical institutions compared to the first evaluation, the test execution proportion is improved (4.87% p increase) - 28.34% of the total, 85.44% of the general hospitals and 20.09% of the clinics
Treatment persistence	Proportion of persistent visiting patients	- 72.02% of the total, 76.60% of advanced general hospitals, 69.70% of clinics
Prescription	Proportion of ICS prescription patients	- The results of all categories of medical institutions improved compared to the first evaluation(5.25% p increase) - 30.62% of the total, 88.20% of the general hospitals and 20.09% of the clinics
	Proportion of essential drug(ICS or LTRA) prescription patients	- Compared with the first evaluation, the proportion of patients who prescribed essential drug(ICS or LTRA) in most categories improved (4.52% p increase) - 63.65% of the total, 96.96% of senior general hospitals, 56.21% of clinics

Fiqure 1. Changes in each of the four evaluation indicators

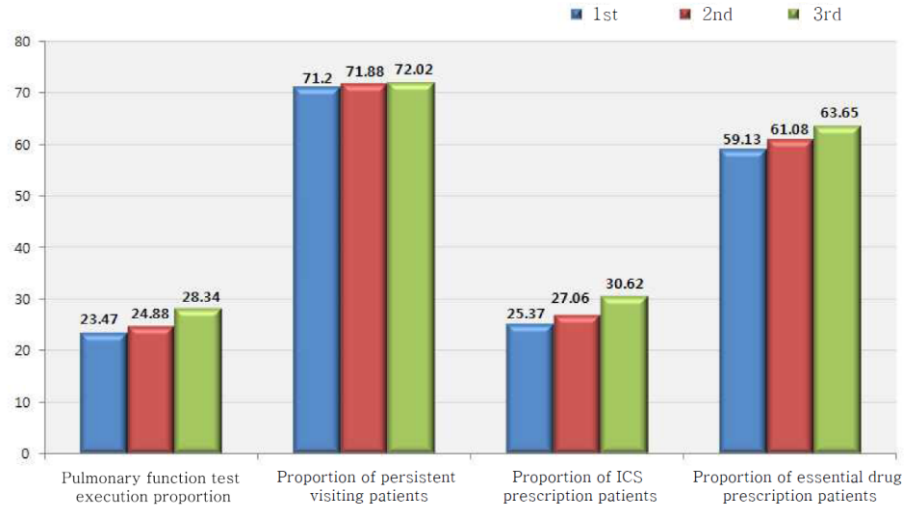


Table 3. Evaluation results by evaluation area

Evaluation area	Name of indicators	Classification of medical institution	2013 year(A)	2014 year	2015 year(B)	B-A
Test	Pulmonary function test execution proportion	Total	23.47	24.88	28.34	4.87
		Advanced general hospital	80.59	81.61	85.44	4.85
		General hospital	59.52	61.30	65.87	6.35
		Hospital	34.83	36.81	38.53	3.70
		Clinic	17.06	18.06	20.09	3.03
Treatment persistence	Proportion of persistent visiting patients	Total	71.20	71.88	72.02	0.82
		Advanced general hospital	75.98	76.76	76.60	0.62
		General hospital	79.22	80.26	80.04	0.82
		Hospital	75.74	77.61	78.09	2.35
		Clinic	69.28	69.76	69.70	0.42
Prescription	Proportion of ICS prescription patients	Total	25.37	27.06	30.62	5.25
		Advanced general hospital	85.94	87.14	88.20	2.26
		General hospital	63.34	65.18	68.60	5.26
		Hospital	31.39	33.71	35.40	4.01
		Clinic	16.42	17.80	20.09	3.67
	Proportion of essential drug(ICS or LTRA) prescription patients	Total	59.13	61.08	63.65	4.52
		Advanced general hospital	95.63	96.40	96.96	1.33
		General hospital	86.77	88.11	89.94	3.17
		Hospital	66.80	70.97	74.2	7.40
		Clinic	52.69	54.47	56.21	3.52
	Proportion of LABA prescription patients without ICS	Total	16.81	18.26	16.77	-0.04
		Advanced general hospital	1.15	0.90	0.63	-0.52
		General hospital	6.03	5.98	4.85	-1.18
		Hospital	15.14	15.69	14.76	-0.38
		Clinic	19.17	21.06	19.91	0.74
	Proportion of SABA prescription patients without ICS	Total	14.34	13.21	12.92	-1.42
		Advanced general hospital	2.42	2.09	1.86	-0.56
		General hospital	7.50	6.62	5.94	-1.56
		Hospital	17.49	15.91	13.73	-3.76
		Clinic	16.02	14.87	15.08	-0.94
	Proportion of OCS prescription patients without ICS	Total	1.18	1.12	28.20	-
		Advanced general hospital	1.07	1.19	3.52	-
		General hospital	2.19	1.99	9.36	-
		Hospital	2.94	2.97	27.15	-
		Clinic	0.96	0.91	33.07	-

3. Method

3.1. Study design

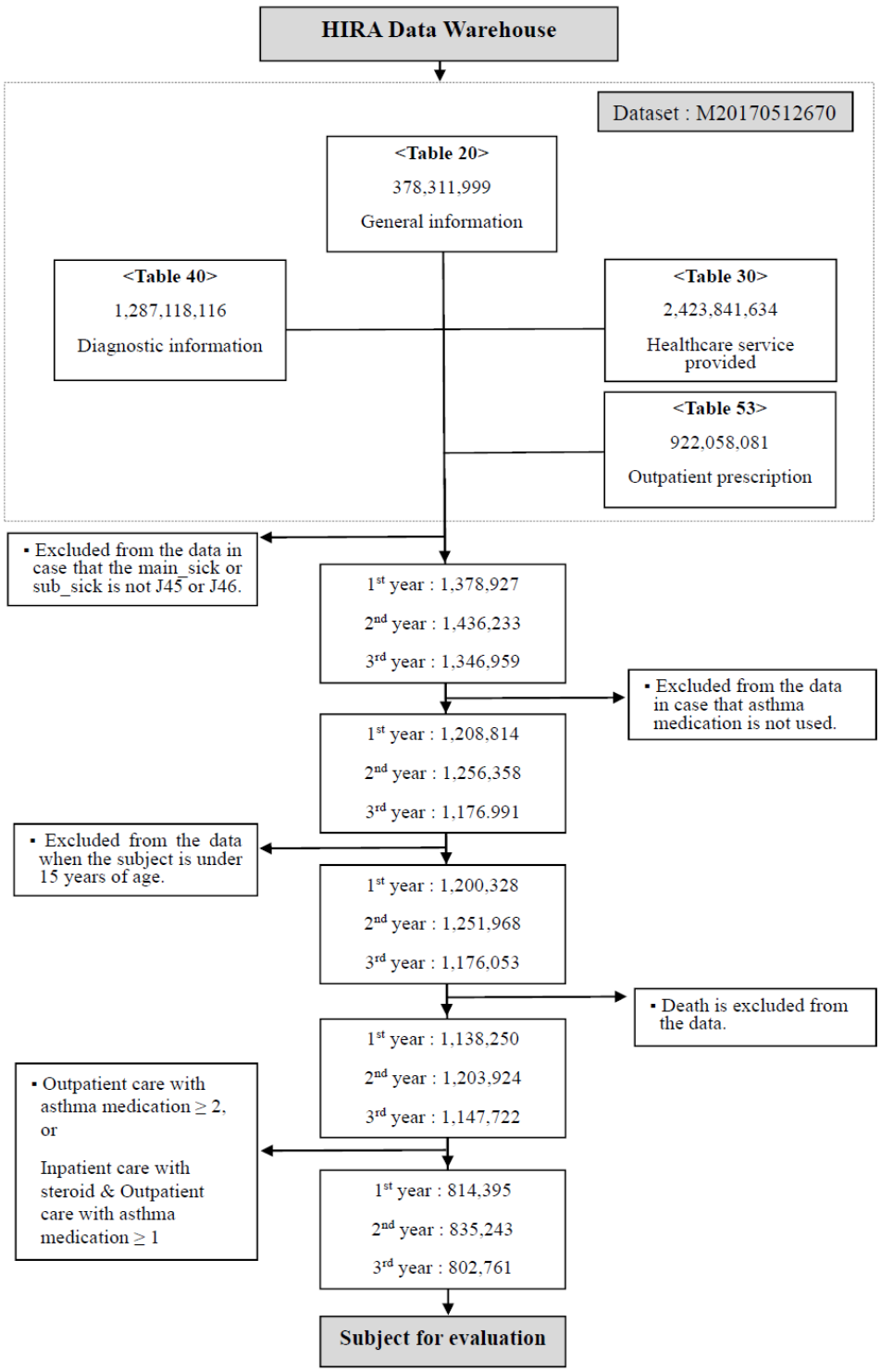
This study used the claim data of HIRA from Asthma patients from July, 2013 to June, 2016 in order to investigate the association between a quality of asthma treatment and an exacerbation of asthma. The registered analysis number of the data requested by HIRA is M20170512670, which is applied to the remote access system and granted access to data on the medical care and prescription of the asthma patients. HIRA provided data from asthma patients 15 years of age or older with a diagnosis code (KCD(Korean Standard Classification of Diseases) code) of J45 or J46 at all medical institution except dental and oriental hospitals. Afterwards, analyses were carried out after eliminating the personally identifiable information from the result of analysis.

The table 20 in the claim data of HIRA contains general information on the socio-demographic information (age, gender, medical aid, etc) and indicators for inpatient and outpatient services. Table 30 is a table for specific information on healthcare service provided (examination, treatment, procedure, prescription medicine, etc.) generated by the patients in the hospital, and table 53 is the details of the outpatient prescription. Table 40 contains a diagnostic information (Kim, L. et al 2014). In the table, the evaluation year is divided into the first year from July 2013 to June 2014, the second year from July 2014 to June 2015, and the third year from July 2015 to June 2016. We also classified asthma patients who were diagnosed as J45 or J46 and those who were 15 years old or older, or who were hospitalized or admitted. Data from table 30 and table 53 were extracted using asthma medications. Among these agents, systemic steroids were classified separately. These data are combined with the data generated from the table 20.

In this study, asthma medicines used in the three evaluation periods were ranked in accordance with the level of controller classified by the GINA guidelines in consultation with the clinicians treating asthma. In addition, the medications used in exacerbation were classified by operational definition and combined with the above data to construct the final data set. In the completed dataset, the subjects for evaluation (patients who had outpatient care using asthma medication more than twice or patients hospitalized with systemic steroids with outpatient care using asthma medication) were extracted. The variables of rank sum, which are the sum of the rank assigned to each asthma medication, and exacerbation were generated and they are compared with the excellent medical institution (or non-excellent medical institution) selected as the evaluation results in HIRA.

This study was conducted under the review of research ethics by the Clinical Research Deliberation Committee of Soon Chun Hyang University Hospital Seoul (IRB approval number: SCHUH-2016-12-004)

Figure 2. The process of extracting the subject for evaluation from the HIRA data warehouse.



3.2. Operational definitions

3.2.1. Asthma medications and their quantitative rank.

The asthma medications were divided into inhaled corticosteroids(ICSs), ICS combined with inhaled long-acting β2-agonists(ICS/LABAs), inhaled short-acting β2-agonists (SABAs), LABAs, anti cholinergics, oral leukotriene receptor antagonists (LTRAs), xanthine derivatives, and systemic corticosteroids. They were ranked in accordance with the level of controller classified by the Global Initiative for Asthma guidelines with the stepwise approach like the following table 4. The Rank-sum variable is the total area multiplied by the duration of the asthma medications and the rank of the medications. And the daily rank-sum of asthma medications is calculated at the individual level. However, if more than one asthma medication is used as different asthma medications at the same time, the sums of their ranks were added up to a maximum of rank 4. High-dose CSs and SABAs were not ranked but were defined as a mark of asthma exacerbation (Koo et al., 2017). Because a high rank sum means that asthma has been poorly controlled and strong medications have been used for a long time, the rank-sum can be a surrogate variable indicating the severity of asthma.

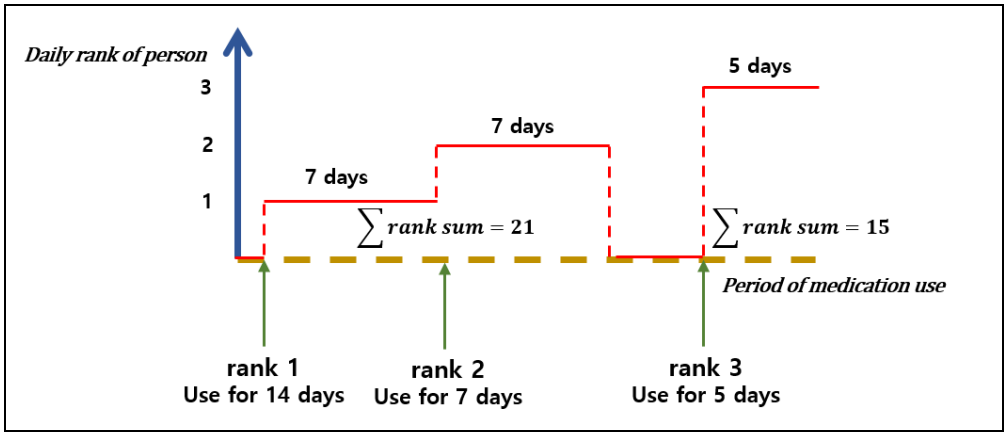
Table 4. Classification of asthma medications and their rank

Rank	Categorization	Classification	ATC codes*
1	ICSs (low-dose)	beclomethasone	R03BA01
		budesonide	R03BA02
		ciclesonide	R03BA08
		fluticasone	R03BA05
	LABA (low-dose)	bambuterol	R03CC12
		clenbuterol	R03CC13
		formoterol	R03CC
		tulobuterol	R03CC11
	LTRA	montelukast	R03DC03
		pranlukast	R03DC02
		zafirlukast	R03DC01

	Xanthine	aminophylline	R03DA05
		bamiphylline	R03DA08
		diethylaminoethyltheophylline	R03DA06
		doxofylline	R03DA11
		oxtriphylline	R03DA02
		theophylline	R03DA04
2	ICSs (medium-to high-dose)	beclomethasone	R03BA01
		budesonide	R03BA02
		fluticasone	R03BA05
	LABA (medium-to high-dose)	formoterol	R03CC
	ICS & LABA	fluticasone & vilanterol	R03AK10
3	ICSs (high-dose)	budesonide	R03BA02
		fluticasone	R03BA05
	ICS & LABA (low-dose)	fluticasone & vilanterol	R03AK10
4	CSs (Less than the amount used when exacerbation)	betamethasone	H02AB01
		deflazacort	H02AB13
		dexamethasone	H02AB02
		hydrocortisone	H02AB09
		methylprednisolone	H02AB04
		prednisolone	H02AB06
	anticholinergic	Tiotropium	R03BB04

* Please refer to the attached appendix1 for the detailed results of rank assignment according to the ATC code of each active ingredient of each medication.

Figure 3. example of rank sum calculation



3.2.2. Asthma exacerbations

Asthma exacerbations is defined as asthma (J45 Asthma or J46 Status asthmaticus in KCD code) when the following asthma exacerbation medications are used:

※ Asthma exacerbation medications: The medicines listed in the table 5 below are from Table 30 (healthcare service provided) and Table 53 (outpatient prescription) as symptom relievers for asthma exacerbations.

: Inhaled steroids reduce hospitalization rates compared with placebo in the treatment of acute asthma exacerbations. Combined inhalants with fast acting sustained beta 2 agonists and inhaled steroids can reduce the use of oral steroids and hospitalization in patients at risk of acute exacerbations. In other words, asthma exacerbation can be prevented if the asthmatic patients are well managed with proper medications.

Table 5. Asthma medications used in exacerbation status

Active ingredient	Code of active ingredient	Note
Betamethasone	116401ATB, 116502BIJ, 116530BIJ	2.4 mg or more as daily dose
Deflazacort	140801ATB	30 mg or more as daily dose
Dexamethasone	141901ATB, 141903ATB, 141904ATB, 142201BIJ, 142202BIJ, 142230BIJ, 142232BIJ	3 mg or more as daily dose
Hydrocortisone	170901ATB, 170905ATB, 170906ATB, 171201BIJ, 171202BIJ	80 mg or more as daily dose
Methylprednisolone	193302ATB, 193305ATB, 193501BIJ, 193502BIJ, 193530BIJ, 193531BIJ, 193601BIJ, 193602BIJ, 193603BIJ, 193604BIJ	16 mg or more as daily dose
Prednisolone	217001ATB, 217003ASY, 217004ASY, 217030ASY, 217034ASY, 217035ASY, 217302BIJ	20 mg or more as daily dose

3.2.3. Hospitalization rate

Asthma hospitalization rate is defined as a hospitalization of patient with J45 Asthma or J46 Asthma persistence status in KCD code

among patients undergoing asthma management at a medical institution

※ Exclusion criteria: If the relationship between hospitalization by asthma and asthma diagnosis is unclear during the evaluation period. It is excluded in case that the asthma hospitalization date is a day diagnosed as asthma during the evaluation period.

3.2.4. Excellent medical institution

: Among the clinics with more than 10 asthmatic patients,

1) Inclusion criteria : Clinics whose outcomes of the four major evaluation indicators are above the median level. (pulmonary function test execution proportion 20% or more, proportion of sustained visiting patients 70% or more, proportion of ICS prescription patients 10%(in case of 1st and 2nd evaluation), 20%(in case of 3rd evaluation*) or more, proportion of essential drugs prescription patients 50% or more)

2) Exclusion criteria : Clinics with the lowest 10% level of the following evaluation indicators (70% or more of LABA prescription patients without ICS, 60% or more of SABA prescription patients without ICS, 5% or more of OCS prescription patients without ICS)

* The inclusion criteria were the same until the second evaluation, and the standard of the criteria was upgraded due to the improvement of asthma evaluation results.

Table 6. Evaluation indicators by HIRA

Evaluation area	Name of indicators	Interpretation of indicators
Test	1. Pulmonary function test execution proportion	The higher the better
Treatment persistence	2. Proportion of persistent visiting patients	
Prescription	3. Proportion of ICS prescription patients 4. Proportion of essential drug(ICS or LTRA) prescription patients	
	5. Proportion of LABA prescription patients without ICS 6. Proportion of SABA prescription patients without ICS 7. Proportion of OCS prescription patients without ICS	The lower the better

3.2.4.1. Execution proportion of pulmonary function test

1) Definition : The percentage of asthmatic patients who underwent one or more pulmonary function tests during the evaluation period

2) Calculation :

$$\frac{Number\ of\ asthma\ patients\ underwent\ pulmonary\ function\ test}{Subject\ number\ for\ evaluation} \times 100$$

3.2.4.2. Proportion of persistent visiting patients

1) Definition : The percentage of asthma patients (persistent visits) who visited the same outpatient clinic more than 3 times during the evaluation period

2) Calculation :

$$\frac{Number\ of\ patients\ who\ visit\ same\ medical\ institution\ more\ than\ 3\ times}{Subject\ number\ for\ evaluation\ of\ treatment\ pesistance*} \times 100$$

*Subject for evaluation of treatment persistence : Patients who received medical treatment at one medical institution during the evaluation period and who used the same institution at the end of the previous year

3.2.4.3. Proportion of ICS prescription patients

1) Definition : The percentage of asthma patients prescribed ICS during the evaluation period

2) Calculation :

$$\frac{Number\ of\ asthma\ patients\ prescribed\ ICS}{Subject\ number\ for\ evaluation} \times 100$$

3.2.4.4. Proportion of patients with essential drug(ICS or LTRA) prescription

1) Definition : The percentage of asthma patients prescribed ICS or LTRA during the evaluation period

2) Calculation :

$$\frac{Number\ of\ asthma\ patients\ prescribed\ ICS\ or\ LTRA}{Subject\ number\ for\ evaluation} \times 100$$

3.2.4.5. Proportion of LABA prescription patients without ICS

1) Definition : The percentage of asthma patients prescribed LABA without ICS during the evaluation period

2) Calculation :

$$\frac{Number\ of\ asthma\ patients\ prescribed\ LABA\ without\ ICS}{Subject\ number\ for\ evaluation} \times 100$$

3.2.4.6. Proportion of SABA prescription patients without ICS

1) Definition : The percentage of asthma patients prescribed SABA without ICS during the evaluation period

2) Calculation :

$$\frac{Number\ of\ asthma\ patients\ prescribed\ SABA\ without\ ICS}{Subject\ number\ for\ evaluation} \times 100$$

3.2.4.7. Proportion of OCS prescription patients without ICS

1) Definition : The percentage of asthma patients prescribed OCS without ICS during the evaluation period

2) Calculation :

$$\frac{Number\ of\ asthma\ patients\ prescribed\ OCS\ without\ ICS}{Subject\ number\ for\ evaluation} \times 100$$

3.3. Objective & Hypotheses

The purpose of this study is to investigate the relationship between asthma treatment and asthma exacerbation of each medical institution for asthmatic patients from July, 2013 to June, 2016 using the claim data provided by HIRA. It is possible to determine the severity of asthma patients according to the rank by assigning a rank to asthma medications. We assessed the severity of asthma patients visiting the excellent medical institution and other non-excellent medical institutions determined according to the HIRA evaluation project, and confirmed the association between each medical institution and the severity of asthma patients. We also investigated the exacerbation of asthma patients based on the use of asthma exacerbation medications and the hospitalization due to asthma, and to investigate the relationship between asthma treatment and asthma exacerbation. In other words, we confirmed the appropriateness of HIRA evaluation indicators by comparing

asthma exacerbation, which was not used in HIRA, with Excellent or Non-excellent medical institutions which are the result of HIRA evaluation. In conclusion, this study is aimed to confirm the appropriateness of the medical care by improving the quality of asthma patient management, reducing the incidence of severe asthma.

The hypotheses to be confirmed through this study are as follows.

1. In the third year of July 2013 through June 2016, asthma patients with a higher asthma severity will visit the excellent medical institutions evaluated under the HIRA's evaluation than other non-excellent medical institutions.

2. However, due to HIRA's evaluation criteria, asthma exacerbation may be less frequent than non-excellent medical institutions.

3. HIRA's criteria will adequately reflect the behavior of medical institutions for asthma treatment.

4. From July 2013 to June 2016, we evaluate the changes of excellent or non-excellent medical institutions in each stage of evaluation for 3 years like the following table 7, and compare them of the hospitalization and the exacerbation of asthma patients in each medical institution. Due to compliance with the guidelines for Korean asthma treatment, hospitalization and asthma exacerbation of asthma patients will be lower as the degree of each year increases.

Table 7. Changes of HIRA evaluation result on medical institutions

Class	Changes of HIRA evaluation result of medical institutions			
Group 1	Non-excellent → Excellent medical institution	1st year : non-excellent	→	2nd year : excellent
			→	3rd year : excellent
		2nd year : non-excellent	→	3rd year : excellent
Group	Excellent → Non-excellent	1st year : excellent	→	2nd year : non-excellent

2	medical institution		→ 3rd year : non-excellent
		2nd year : excellent	→ 3rd year : non-excellent
Group 3	Non-excellent → Non-excellent medical institution	1st year : non-excellent	→ 2nd year : non-excellent
			→ 3rd year : non-excellent
		2nd year : non-excellent	→ 3rd year : non-excellent
Group 4	Excellent → Excellent medical institution	1st year : excellent	→ 2nd year : excellent
			→ 3rd year : excellent
		2nd year : excellent	→ 3rd year : excellent

3.4. Statistical methods

In hypothesis 1, 2, and 4, the relationship between severity of asthma and asthma exacerbations and the evaluation results by HIRA is evaluated through comparison.

In hypothesis 3, the relationship between asthma exacerbation rate and excellent / non-excellence medical institutions, which is calibrated for severity of asthma by the rank sum, is determined using the linear regression equation(log logistic distribution) as shown below. If the value of $\beta 2$ is significantly negative, when it is calibrated by the rank sum, it can be judged that the evaluation results by HIRA evaluation indicators adequately reflect asthma exacerbation.

Analysis was performed using SAS 9.4.

[Calculation]

$$log\breve{Y}_i = \beta_0 + \beta_1 \times rank\ \ sum + \beta_2\ \times excellence_j + \epsilon_1$$

- $\breve{Y}_i$: exacerbation rate by medical institution, i = each medical institution
- rank sum : average daily rank sum of patients visited a i^{th} medical institution a year
- excellence $_j$: excellence medical institution(j = 1), non-excellence medical institution(j = 0)
- ε_1 : the error term

4. Results

1. Prescription Patterns of Asthma medications

The quantitative distribution of asthma medications prescribed during the evaluation period of the third trimester from July 2013 to June 2016 and the use of asthma exacerbations are shown in the table 8, 9, 10. All of the third year shows similar medication use patterns. Medications of rank 1 such as ICS, LTRA and Xanthine were the most frequently used like 1st year (59.67%), 2nd year (59.68%) and 3rd year (58.58%), followed by Rank 0 drugs such as SABA and systemic steroids like 1st year (20.68%), 2nd year (20.10%) and 3rd year (20.20%). The inpatient prescriptions (table 30) and outpatient prescriptions (tables 53) showed different prescription patterns. In the case of inpatient prescription, Rank 0, Rank 1 and Rank 4 were the order of the all three years, and Rank 1, Rank 4, Rank 0 were the order of outpatient prescription.

Over the three-year period, the use of asthma exacerbation drugs showed similar patterns of use like 1st year (10.9%), 2nd year (10.76%) and 3rd year (10.81%). However, the use of exacerbation drugs between inpatient and outpatient prescriptions showed a great difference. In the case of inpatient prescriptions, the use of exacerbation drugs was much higher like 1st year (47.34%), 2nd year (46.77%) and 3rd year (46.66%) than outpatient prescriptions like 1st year (2.59%), 2nd year (2.43%) and 3rd year (2.58%).

Table 8. Distribution of quantitative asthmatic medication and asthma exacerbation drug use in 1st evaluation period

	Rank						Exacerbation		
	0	1	2	3	4	Total	0	1	Total
In-patient prescription from 30 table(A)	771,897 (51.76)	666,897 (44.72)	6,455 (0.11)	1,638 (0.11)	44,397 (2.98)	1,491,284 (100.00)	785,279 (52.66)	706,005 (47.34)	1,491,284 (100.00)
Out-patient prescription from 53 table(B)	889,881 (13.60)	4,126,976 (63.08)	437,263 (6.68)	766,81 (1.17)	1,011,661 (15.46)	654,2462 (100.00)	6,373,144 (97.41)	169,318 (2.59)	654,2462 (100.00)
A + B	1,661,778 (20.68)	4,793,873 (59.67)	443,718 (5.52)	1,638 (0.02)	1,056,058 (13.15)	8,033,746 (100.00)	7,158,423 (89.10)	875,323 (10.90)	8,033,746 (100.00)

Table 9. Distribution of quantitative asthmatic medication and asthma exacerbation drug use in 2nd evaluation period

	Rank						Exacerbation		
	0	1	2	3	4	Total	0	1	Total
In-patient prescription from 30 table(A)	795,277 (51.37)	691,769 (44.68)	7,107 (0.46)	1,737 (0.11)	52,219 (3,37)	1,548,109 (100.00)	824,214 (53.23)	723,985 (46.77)	1,548,109 (100.00)
Out-patient prescription from 53 table(B)	860,361 (12.86)	4,224,180 (63.15)	482,064 (7.21)	88,689 (1.33)	1,033,446 (15.45)	6,688,740 (100.00)	6,526,042 (97.57)	162,698 (2.43)	6,688,740 (100.00)
A + B	1,655,638 (20.10)	4,915,949 (59.68)	489,171 (5.94)	90,426 (1.10)	1,085,665 (13.18)	8,236,849 (100.00)	7,350,256 (89.24)	886,683 (10.76)	8,236,849 (100.00)

Table 10. Distribution of quantitative asthmatic medication and asthma exacerbation drug use in 3rd evaluation period

	Rank						Exacerbation		
	0	1	2	3	4	Total	0	1	Total
In-patient prescription from 30 table(A)	766,226 (51.69)	653,758 (44.11)	7,384 (0.50)	1,855 (0.13)	52,986 (3.57)	1,482,209 (100.00)	790,654 (53.34)	691,555 (46.66)	1,482,209 (100.00)
Out-patient prescription from 53 table(B)	837,657 (12.97)	3,996,631 (61.90)	560,572 (8.68)	100,915 (1.56)	960,715 (14.88)	6,456,490 (100.00)	6,289,659 (97.42)	166,831 (2.58)	6,456,490 (100.00)
A + B	1,603,883 (20.20)	4,650,389 (58.58)	567,956 (7.15)	102,770 (1.29)	1,013,701 (12.77)	7,938,699 (100.00)	7,080,313 (89.19)	858,386 (10.81)	7,938,699 (100.00)

2. Distribution of asthma patients by medical institution

1) Distribution of asthma patients by medical institution

The distribution of visiting asthma patients in each evaluation year is shown in Table 11. In all three years, the number of visiting clinic patients was the highest as 1st year (956,557), the 2nd year (1,005,766), and the 3rd year (933,787), followed by general hospitals, hospitals, and tertiary hospitals. In case of the average annual rank sum of asthma patients, tertiary hospital was the highest as 1st year (0.7575), 2nd year (0.7622), and 3rd year (0.8051), respectively, followed by general hospitals, community health center branch office, and regional medical center. Clinic was the lowest as 1st year (0.2216), 2nd year (0.2193), and 3rd year (0.2374), respectively.

In terms of the annual use of asthma exacerbation drug, the hospital was the highest as 1st year (0.4820), 2nd year (0.4834), 3rd year (0.4835), followed by regional medical centers, general hospitals, hospitals.

Table 11. Association between the rank-sum and the category of medical institutions

Evaluation period	Category of medical institution	Number of patients	The average annual rank-sum of asthma patients	SD
1st	Tertiary hospital	60,087	0.7575	0.8358
	General hospital	118,607	0.6376	0.8569
	Hospital	71,227	0.4578	0.8164
	Long term care hospital	4,449	0.4001	0.8367
	Clinics	956,557	0.2216	0.4918
	Community health center	3,551	0.4613	0.6874
	Community health center, branch office	813	0.6236	0.8943
	Regional medical center	744	0.5828	0.7814
2nd	Tertiary hospital	66,380	0.7622	0.8435
	General hospital	126,313	0.6377	0.8467
	Hospital	75,930	0.4477	0.7921

	Long term care hospital	4,357	0.3952	0.8250
	Clinics	1,005,766	0.2193	0.4840
	Community health center	3,312	0.4489	0.7132
	Community health center, branch office	800	0.5774	0.8106
	Regional medical center	864	0.5534	0.7949
3rd	Tertiary hospital	72,319	0.8051	0.8550
	General hospital	138,600	0.6615	0.8506
	Hospital	74,744	0.4643	0.8063
	Long term care hospital	3,894	0.4276	0.8349
	Clinics	933,787	0.2374	0.5056
	Community health center	2,515	0.5061	0.7421
	Community health center, branch office	708	0.5777	0.7879
	Regional medical center	740	0.6196	0.8597

Table 12. Association between the asthma exacerbation medication use among visited patients and the category of medical institutions

Evaluation period	Category of medical institution	Number of patients	The annual asthma exacerbation medication use among visited patients	SD
1st	Tertiary hospital	60,087	0.3146	0.4644
	General hospital	118,607	0.3541	0.4782
	Hospital	71,227	0.4820	0.4997
	Long term care hospital	4,449	0.2782	0.4482
	Clinics	956,557	0.3007	0.4584
	Community health center	3,551	0.2202	0.4144
	Community health center, branch office	813	0.2029	0.4024
	Regional medical center	744	0.4167	0.4933
2nd	Tertiary hospital	66,380	0.3046	0.4602
	General hospital	126,313	0.3490	0.4767
	Hospital	75,930	0.4834	0.4997
	Long term care hospital	4,357	0.2613	0.4394
	Clinics	1,005,766	0.2903	0.4539
	Community health center	3,312	0.2110	0.4081
	Community health center, branch office	800	0.2413	0.4282
	Regional medical center	864	0.3808	0.4859
3rd	Tertiary hospital	72,319	0.2978	0.4573
	General hospital	138,600	0.3404	0.4738

	Hospital	74,744	0.4835	0.4997
	Long term care hospital	3,894	0.2606	0.4390
	Clinics	933,787	0.2914	0.4543
	Community health center	2,515	0.1960	0.3970
	Community health center, branch office	708	0.2127	0.4095
	Regional medical center	740	0.3743	0.4843

2) Distribution of asthma patients with excellent / non-excellent medical institutions according to the results of the HIRA

The average annual rank sum of asthma patients visiting the excellent institution was higher than the one of asthma patients visiting non-excellent institution as 1st year (0.3726), 2nd year (0.3654), and 3rd year (0.3984). As shown in Table 13, the average exacerbation from the exacerbation drug use in asthma patients visiting the excellent institution was higher than non-excellent institution as 1st year (0.3409), 2nd year (0.3328), and 3rd year (0.3265), respectively. Likewise, considering the asthma exacerbation due to hospitalization of asthma patients, the hospitalization of excellent institution was higher than that of non-excellent institution as 1st year (0.0209), 2nd year (0.0200), and 3rd year (0.0193). The severity of asthma has a tendency to increase from the 1st to the 2nd to the 3rd year, with asthma exacerbations showing a tendency to decrease.

Table 13. Association between the average annual rank-sum and the result of HIRA evaluation

Evaluation period	HIRA evaluation result	Number of patients	The average annual rank-sum of asthma patients	SD
1st evaluation	Non-excellent	880,802	0.2065	0.4755
	Excellent	95,157	0.3726	0.6111
2nd evaluation	Non-excellent	908,545	0.2013	0.4641
	Excellent	119,703	0.3654	0.6024
3rd evaluation	Non-excellent	831,360	0.2146	0.4803
	Excellent	125,173	0.3984	0.6342

Table 14. Association between asthma exacerbation and the result of HIRA evaluation

Evaluation period	HIRA evaluation result	Number of patients	The average exacerbation of asthma patients			
			Asthma medications	SD	Hospitalization	SD
1st	Non-excellent	880,802	0.2963	0.4566	0.0129	0.1127
	Excellent	95,157	0.3409	0.474	0.0209	0.1430
2nd	Non-excellent	908,545	0.2850	0.4514	0.0129	0.1130
	Excellent	119,703	0.3328	0.4713	0.0200	0.1401
3rd	Non-excellent	831,360	0.2864	0.4521	0.0134	0.1153
	Excellent	125,173	0.3265	0.4689	0.0193	0.1376

3. Association of the asthma exacerbation rate and evaluation of medical institution by HIRA

As a result of confirming the relationship between asthma exacerbation rate and rank sum, it was confirmed that rank sum and asthma exacerbation rate were significantly correlated with each other as in Model 1 of Tables 15, 16 and 17. The asthma exacerbation rate increases in the 1st year (13.3 % increase), the 2nd year (18.2% increase) and the 3rd year (21.9% increase) when rank sum increases by 1. As a result of confirming the relationship between the asthma exacerbation rate and the evaluation of the medical institution (excellent / non-excellent medical institution), as in Model 2 of Tables 15, 16, and 17, it was confirmed that the excellent medical institution and asthma exacerbation rate were significantly correlated with each other except for the results of 1st year. However, in Model 3, the positive correlation between the excellent medical institution and the rate of asthma exacerbation were not significant in all three years.

Table 15. Effect of average daily rank sums of patients visited selected clinics and asthma evaluation of the clinics on asthma exacerbation rates in 1st evaluation period (July, 2013~June, 2014)

	Model 1			Model 2			Model 3		
	P.E	SE	p-value	P.E	SE	p-value	P.E	SE	p-value
β_0	-1.1887	0.0075	< .0001	-1.1462	0.0070	<.0001	-1.1907	0.0078	<.0001
β_1	0.1332	0.0087	< .0001	-	-	-	0.1331	0.0087	<.0001
β_2	-	-	-	0.0394	0.0265	0.1373	0.0303	0.0264	0.2500
AIC	4151.0978			4274.3068			4151.8089		

β_0 : y intercept
β_1 : average daily rank sums of patients visited selected clinics
β_2 : asthma evaluation

Table 16. Effect of average daily rank sums of patients visited selected clinics and asthma evaluation of the clinics on asthma exacerbation rates in 2nd evaluation period (July, 2014~June, 2015)

	Model 1			Model 2			Model 3		
	P.E	SE	p-value	P.E	SE	p-value	P.E	SE	p-value
β_0	-1.2320	0.0080	<.0001	-1.1743	0.0072	<.0001	-1.2352	0.0082	<.0001
β_1	0.1824	0.0101	<.0001	-	-	-	0.1823	0.0101	<.0001
β_2	-	-	-	0.0548	0.0247	0.0265	0.0405	0.0246	0.0992
AIC	4137.8864			4315.7868			4137.2585		

β_0 : y intercept
β_1 : average daily rank sums of patients visited selected clinics
β_2 : asthma evaluation

Table 17. Effect of average daily rank sums of patients visited selected clinics and asthma evaluation of the clinics on asthma exacerbation rates in 3rd evaluation period (July, 2015~June, 2016)

	Model 1			Model 2			Model 3		
	P.E	SE	p-value	P.E	SE	p-value	P.E	SE	p-value
β_0	-1.2558	0.0083	<.0001	-1.1827	0.0072	<.0001	-1.2582	0.0086	<.0001
β_1	0.2187	0.0112	<.0001	-	-	-	0.2185	0.0112	<.0001
β_2	-	-	-	0.0513	0.0237	0.0300	0.0289	0.0235	0.2198
AIC	3911.4662			4115.8297			3911.9960		

β_0 : y intercept
β_1 : average daily rank sums of patients visited selected clinics
β_2 : asthma evaluation

4. Effectiveness of HIRA project to evaluate asthma care

When considering the relationship between the change of evaluation results and the rank sum in the table 18, and the rank sum difference for each year increased from the 1st year to the 2nd year, the 1st year to the 3rd year, and the 2nd year to the 3rd year in group 1, 3 and 4. By the way, in case of asthma exacerbation judged by the asthma exacerbation drug use, there was a decrease from 1st year to 2nd year, from 1st year to 3rd year, from 2nd year to 3rd year in all group. In case of asthma exacerbations judged by asthma hospitalization, it was found that the hospitalization increased in group 1, which changed from non-excellent to excellent medical institution. On the other hand, group 2, which changed from excellent to non-excellent medical institution, shows the decrease of asthma hospitalization.

Table 18. Association between the change of HIRA evaluation result and rank-sum and asthma exacerbation and hospitalization

Group 1. Non-excellent → Excellent medical institution

change of HIRA evaluation result of medical institution			Difference in		
			rank-sum (S.D)	Exacerbation (S.D)	Hospitalization (S.D)
1st year : non-excellent	→	2nd year : excellent	0.0153 (0.0919)	-0.0070 (0.0804)	0.0033 (0.0315)
	→	3rd year : excellent	0.0427 (0.1137)	-0.0276 (0.1058)	0.0012 (0.0308)
2nd year : non-excellent	→	3rd year : excellent	0.0327 (0.1001)	-0.0051 (0.0842)	0.0029 (0.0272)

Group 2. Excellent → Non-excellent medical institution

change of HIRA evaluation result of medical institution			Difference in		
			rank-sum (S.D)	Exacerbation (S.D)	Hospitalization (S.D)
1st year : excellent	→	2nd year : non-excellent	-0.0120 (0.0992)	-0.0241 (0.0866)	-0.0021 (0.0349)

	→	3rd year : non-excellent	0.0012 (0.1150)	-0.0299 (0.0913)	-0.0027 (0.0327)
2nd year : excellent	→	3rd year : non-excellent	-0.0079 (0.0894)	-0.0228 (0.0713)	-0.0054 (0.0277)

Group 3. Non−excellent → Non−excellent medical institution

change of HIRA evaluation result of medical institution			Difference in		
			rank-sum (S.D)	Exacerbation (S.D)	Hospitalization (S.D)
1st year : non-excellent	→	2nd year : non-excellent	-0.0018 (0.2537)	-0.0110 (0.1826)	-0.0013 (0.0850)
	→	3rd year : non-excellent	0.0111 (0.2590)	-0.0155 (0.1863)	0.0000 (0.0836)
2nd year : non-excellent	→	3rd year : non-excellent	0.0112 (0.2640)	-0.0066 (0.1815)	0.0011 (0.0889)

Group 4. Excellent → Excellent medical institution

change of HIRA evaluation result of medical institution			Difference in		
			rank-sum (S.D)	Exacerbation (S.D)	Hospitalization (S.D)
1st year : excellent	→	2nd year : excellent	0.0103 (0.0705)	-0.0172 (0.0662)	0.0012 (0.0240)
	→	3rd year : excellent	0.0193 (0.0779)	-0.0314 (0.0797)	-0.0024 (0.0278)
2nd year : excellent	→	3rd year : excellent	0.0133 (0.0705)	-0.0171 (0.0698)	-0.0036 (0.0239)

5. Discussion

The Korean Asthma Care Guideline and the GINA Guidelines are designed to use ICS and LTRA as first-line treatment for asthma treatment. When we look at the actual prescribed asthma medicines in each medical institution in Korea, we found that the first-line asthma medications are used the most as about 60% based on table 8, 9 and 10. One of the interesting thing is that Rank 0 occupies a large portion followed by Rank 1. It is considered that SABA and systemic steroids (asthma exacerbation drug) were used. Of the total prescription, we could confirm that asthma exacerbation drug was overwhelmingly prescribed in inpatient prescription than outpatient prescription, because patients in the hospital are more severe than those outside the hospital.

The rank sum of the tertiary hospitals was the highest among the medical institutions, and the general hospital was next in table 11. The results show us that our hypothesis that asthma patients with high severity visited the tertiary hospitals or general hospitals is correct. And the number of patients visiting clinics among the medical institutions is the highest. The lowest rank sum of asthma patients visiting the clinic means that mild patients visit the clinic. However, asthma exacerbation rate was not low in the clinic compared with other institutions based on table 12. It is likely that mild patients visited the clinic, but asthma management was not going well. In addition, the severity of these poorly managed patients is increasing, suggesting that these patients visit more advanced medical institutions.

Unlike the hypothesis that asthma exacerbation is low due to good management of asthma patients in case of excellent medical institution selected by HIRA evaluation, the asthma exacerbation rate due to the asthma hospitalization and asthma exacerbation drug use is higher in the excellent medical institution compared to non-excellent institution based on table 14. Because there are more

asthma patients with high severity in excellent medical institution than non-excellent institution, it is expected that asthma exacerbation rate in excellent medical institution is higher than non-excellent medical institution. Considering it, we analyzed the association between asthma exacerbations and excellent medical institution using a linear model with the log normal distribution, considering the severity of asthma. As a result, there was a significant positive correlation between the degree of asthma exacerbation and excellent medical institution, but the results were not significantly positive when considering asthma severity. It means that we can not know the correlation between the HIRA evaluation results and asthma exacerbation, when we calibrate the severity of asthma. This was an unexpected and different result from our hypothesis that the excellent medical institution evaluated by HIRA can show the good management of asthma care.

In terms of the evaluation of asthma quality management according to the changes of the evaluation periods in table 18, asthma exacerbation decreased in all four groups. It was easily understandable that exacerbation was reduced in group 1, which changed from a non-excellent medical institution to an excellent medical institution, because the management of asthma patients in an excellent medical institution was well managed. However, it is not easily understood that exacerbation is also reduced in group 2, which changes from excellent medical institution to non-excellent medical institution. Exacerbation was reduced in all groups as well as in groups 1 and 2, which means that the use of asthma exacerbation drugs decreased with increasing year regardless of excellent or non-excellent medical institutions. This may mean that the asthma management was adequately controlled without the use of asthma exacerbation drugs, due to improved management of asthma care, such as increased use of ICS. On the other hand, this result may be interpreted as showing that the evaluation results of HIRA are not related to asthma exacerbation. This suggests that HIRA's evaluation indicators may have helped improve asthma care

in medical institutions but may not be appropriate indicators to assess whether asthma care has improved or not. Asthma hospitalization was increased in group 1, which changed from non-excellent medical institution to excellent medical institution, and hospitalization was decreased in group 2, which is the opposite, suggesting high hospitalization rate is related to excellent medical institution. The high hospitalization rate of an excellent medical institution also suggests that the HIRA evaluation result does not adequately reflect the hospitalization resulting from asthma treatment. Because the asthma evaluation by HIRA is made up of evaluation indicators that primarily confirm compliance with the Korean guideline of asthma, HIRA's evaluation indicators seem to have limitations that do not contribute to preventing hospitalization due to asthma. Therefore, it may be necessary to improve the asthma evaluation indicators of HIRA evaluation project as a way to prevent asthma hospitalization practically, such as the rate of hospitalization due to asthma or visit to the emergency room, as well as evaluation of asthma medications as in foreign cases.

Although this study is a meaningful study analyzing the correlation between the quality of asthma treatment and asthma exacerbation, there are some limitations as follows. Although the subjects were classified according to the HIRA criteria for evaluation, there was no correction for age, sex, and underlying diseases like atopic and allergic diseases at the individual level, and no multi-level analysis was performed reflecting the regional characteristics of the medical institution. Older age, female, and geographical differences are considered to be risk factors for asthma. Women have a higher prevalence of asthma than men and older people aged over 70 have a higher prevalence of asthma than other age groups. In addition, the prevalence of asthma in the elderly was high when there were underlying diseases such as chronic obstructive pulmonary disease(COPD)(Kim et al. 2013). Jackson et al reported that viruses, seasonal patterns, virus-allergic interactions, pollutions(NO_2, particulate matter, ozone, and sulfur dioxide),

smoking, pregnancy, and stress were associated with asthma exacerbations(Jackson, Sykes et al. 2011). In addition, the incidence of asthma among elderly people aged 65 years or older was significantly different according to the size of the city, and the incidence of asthma was significantly higher in metropolitan cities than in small cities and rural areas(김문년, 이원기 et al. 2013). It is also expected that the pattern of prescribing according to the region of the medical institution will be different. For example, it is expected that the prescription of oral steroids will be more popular in the rural clinics than in the big cities.

The difficulty of analyzing big data in health care area is also considered as a limit of this study. HIRA 's claim data is a big data. It is difficult to understand the characteristics of data and it is not easy to carry out scientific analysis using it. For example, since asthma patients do not visit a single medical institution, an individual may visit several medical institutions. It was also found that there was a change in the results of the HIRA evaluation due to the moving of the medical institution. In addition, since the way of filling the dosage and days of some drug use in claim data is different for each medical institution, we have to know how to fill them and the reason of difference for calculation of rank sum. And the data was so large that we had an unexpected and unintelligible outcome, and we had to think about whether to include it in the analysis or outlier it. Based on the advice of HIRA's claim data expert and asthma treatment clinician, we had to determine the direction of analysis. In other words, the analysis of big data may show different results depending on how the variables are set or corrected, and how the missing values or outliers are processed.

In spite of many limitations, this study is a scientific analysis of the association between the quality of asthma treatment and the exacerbation rate through the relationship between asthma evaluation indicators of HIRA and asthma exacerbation. Although this study did not elucidate causality between the evaluation

indicators by HIRA and asthma exacerbations, it is meaningful that it raised questions about the need for improvement of asthma evaluation indicators of HIRA. The results of the study are expected to be reflected in the project of HIRA for evaluation of appropriateness of asthma care institutions, which affect the asthma care behavior of medical institutions.

In future studies, it is necessary to investigate the causality through multilevel analysis including individual and regional correction, and to find the evaluation indicators that can confirm improvement of asthma treatment as well as improvement of asthma treatment by HIRA indicators. For example, it is expected that the quality of asthma care can be improved by improving the evaluation indicators of HIRA as a way to prevent asthma hospitalization.

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Abstract

기관별 천식 진료의 질과 악화율의 상관성 분석

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배경/목적: 건강보험심사평가원은 2013년부터 요양기관의 천식 진료 행위의 적정성과 요양급여의 비용효과적인 측면을 고려하여 천식 진료 요양기관의 적정화 평가 사업을 추진하였다. 하지만 천식 질환에 대하여 건강보험심사평가원에서 수행한 요양기관 평가 결과의 적정성을 확인한 연구는 아직 없는 상황이다. 본 연구에서는 건강보험심사평가원의 청구 데이터를 활용하여, 건강보험심사평가원의 요양기관 평가 결과와 천식 진료의 질의 상관성을 확인하고자 한다.

방법: 본 연구에는 2013년 7월 1일부터 2016년 6월 30일까지의 천식환자의 건강보험심사평가원 청구데이터를 활용하였다. 건강보험심사평가원 청구 자료의 분석 과제 번호는 M20170512670으로 원격 접속 시스템 신청 과정을 거쳐 전체 요양기관에서 천식(J45) 또는 천식지속상태(J46)를 주상병 또는 제1부상병으로 하는 15세 이상의 대상자에 대한 자료 접속 권한을 부여 받았다. 건강보험심사평가원 청구데이터인 20테이블(일반정보), 30테이블(진료 내역) 및 53테이블(처방전 내역)을 통해 천식 약제 사용 정보와 천식 환자를 추출하였다. 또한 천식 악화 시 사용하는 약제를 결정하고, 천식 약제들에 부여한 약제 별 rank의 합을 산출하였다. 건강보험심사평가원의 의료기관 별 천식 진료 평가 결과를 천식 악화율과의 회귀분석을 통해 상관성을 분석하였다.

결과: 건강보험심사평가원의 요양기관에 대한 평가가 적절히 수행되었다면, 평가 결과가 양호한 기관일수록 천식 악화 시 사용하는 약제 사용이 적고 천식으로 인한 입원률이 낮아서 천식 악화율이 적을 것이다. 하지만 이러한 가설과는 달리 평가 양호 기관과 천식 악화율은 유의한 상관관계를 나타내지 않았다. 게다가 천식 악화 약제 사용으로 인한 천식 악화율은 평가 차수가 지날수록 지속적으로 감소하였고, 천식 입원률은 평가 양호 기관일수록 높게 나타나는 경향을 보여주었다.

결론: 이 결과는 건강보험심사평가원의 천식 요양기관 평가가 천식 악화 시 사용하는 약제의 사용 감소를 유도하여 요양기관의 천식 진료의 질을 향상시킨 것으로 보이지만, 천식 진료의 효과가 적절히 평가 기준에 반영되지는 않았음을 시사한다. 본 연구결과는 건강보험심사평가원의 천식 요양기관 적정화 사업에 반영되어 평가 기준 지표 설정의 제고 및 요양기관의 천식 진료 행태에 영향을 미칠 수 있을 것으로 기대한다.

주요어 : 천식, 악화, 천식 진료의 질, 적정성 평가, 한국
학번 : 2015-24005

Appendix 1. Detailed results of rank assignment according to the ATC code of each active ingredient of each asthma medications

Gnl_cd	Class	Gnl_name	Admin	1st_yr	2nd_yr	3rd_yr	Excerbation	period	Rank
107301ATB	Xanthine	aminophylline	oral	1	1	1	0	1	1
107301ATR	Xanthine	aminophylline	oral	1	1	1	0	1	1
107302BIJ	Xanthine	aminophylline	iv	1	1	1	0	1	1
107303ATR	Xanthine	aminophylline	oral	1	1	1	0	1	1
107330BIJ	Xanthine	aminophylline	iv	0	0	1	0	1	1
113601ATB	LABA	bambuterol	oral	1	1	1	0	1	1
113602ASY	LABA	bambuterol	oral	1	1	1	0	1	1
113630ASY	LABA	bambuterol	oral	0	0	1	0	1	1
113801ATB	Xanthine	bamiphylline	oral	1	1	1	0	1	1
113802ATB	Xanthine	bamiphylline	oral	1	1	1	0	1	1
114508CSI	CS	beclomethasone	inhaled	1	1	1	0	1	1
114509CSI	CS	beclomethasone	inhaled	1	1	1	0	1	1
114510CSI	CS	beclomethasone	inhaled	1	1	1	0	1	1
114530CSI	CS	beclomethasone	inhaled	0	0	1	0	1	1
114532CSI	CS	beclomethasone	inhaled	0	0	1	0	1	1
114533CSI	CS	beclomethasone	inhaled	0	0	1	0	1	1
116401ATB	CS	betamethasone	oral	1	1	1	1	1	4
116502BIJ	CS	betamethasone	iv	1	1	1	1	1	4
116530BIJ	CS	betamethasone	iv	0	0	1	1	1	4
119404CSI	CS	budesonide	inhaled	1	1	1	0	1	1
119407CAE	CS	budesonide	inhaled	1	1	0	0	30	1
119438CAE	CS	budesonide	inhaled	0	0	1	0	30	1
119502CSI	CS	budesonide	inhaled	1	1	1	0	30	1
119505CSI	CS	budesonide	inhaled	1	1	1	0	30	1
119506CSI	CS	budesonide	inhaled	1	1	1	0	30	2
119530CSI	CS	budesonide	inhaled	0	0	1	0	30	1
119531CSI	CS	budesonide	inhaled	0	0	1	0	30	1
119532CSI	CS	budesonide	inhaled	0	0	1	0	30	2
119533CSI	CS	budesonide	inhaled	0	0	1	0	1	1
135301ASY	LABA	clenbuterol	oral	1	1	1	0	1	1
135330ASY	LABA	clenbuterol	oral	0	0	1	0	1	1
135331ASY	LABA	clenbuterol	oral	0	0	1	0	1	1
140801ATB	CS	deflazacort	oral	1	1	1	1	1	4
141901ATB	CS	dexamethasone	oral	1	1	1	1	1	4
141903ATB	CS	dexamethasone	oral	1	1	1	1	1	4
141904ATB	CS	dexamethasone	oral	0	1	1	1	1	4
142201BIJ	CS	dexamethasone	iv	1	1	1	1	1	4
142202BIJ	CS	dexamethasone	iv	1	1	1	1	1	4
142230BIJ	CS	dexamethasone	iv	0	0	1	1	1	4
142232BIJ	CS	dexamethasone	iv	0	0	1	1	1	4
144001ATB	Xanthine	diethylaminoethyltheophylline	oral	1	1	0	0	1	1
157901ATB	SABA	fenoterol	oral	1	1	1	0	1	0
157902CLQ	SABA	fenoterol	inhaled	1	1	1	0	1	0
157930CLQ	SABA	fenoterol	inhaled	0	0	1	0	1	0
162202CSI	CS	fluticasone	inhaled	1	1	1	0	30	2
162203CSS	CS	fluticasone	inhaled	1	1	1	0	30	1
162204CSI	CS	fluticasone	inhaled	1	1	1	0	30	2
162205CSI	CS	fluticasone	inhaled	1	1	1	0	30	1
162206CSS	CS	fluticasone	inhaled	1	1	1	0	1	3
162230CSS	CS	fluticasone	inhaled	0	0	1	0	1	3
162231CSS	CS	fluticasone	inhaled	0	0	1	0	1	1
162232CSI	CS	fluticasone	inhaled	0	0	1	0	30	1
162233CSI	CS	fluticasone	inhaled	0	0	1	0	30	1
162235CSI	CS	fluticasone	inhaled	0	0	1	0	30	2
162236CSI	CS	fluticasone	inhaled	0	0	1	0	30	2
163101ASY	LABA	formoterol	oral	1	1	0	0	1	1
163101ATB	LABA	formoterol	oral	1	1	1	0	1	1
163104ASY	LABA	formoterol	oral	1	1	1	0	1	1
163104ATB	LABA	formoterol	oral	1	1	1	0	1	1
163130ASY	LABA	formoterol	oral	0	0	1	0	1	1
163131ASY	LABA	formoterol	oral	0	0	1	0	1	1
170901ATB	CS	hydrocortisone	oral	1	1	1	1	1	4
170905ATB	CS	hydrocortisone	oral	1	0	0	1	1	4
170906ATB	CS	hydrocortisone	oral	1	1	1	1	1	4
171201BIJ	CS	hydrocortisone	iv	1	1	1	1	1	4

171202BIJ	CS	hydrocortisone	iv	1	1	1	1	1	4
177101CLQ	anticholinergic	ipratropium	inhaled	1	1	1	0	1	0
177103CLQ	anticholinergic	ipratropium	inhaled	1	1	1	0	1	0
177131CLQ	anticholinergic	ipratropium	inhaled	0	0	1	0	1	0
193302ATB	CS	methylprednisolone	oral	1	1	1	1	1	4
193305ATB	CS	methylprednisolone	oral	1	1	1	1	1	4
193501BIJ	CS	methylprednisolone	iv	1	1	1	1	1	4
193502BIJ	CS	methylprednisolone	iv	1	1	1	1	1	4
193530BIJ	CS	methylprednisolone	iv	0	0	1	1	1	4
193531BIJ	CS	methylprednisolone	iv	0	0	1	1	1	4
193601BIJ	CS	methylprednisolone	iv	1	1	1	1	1	4
193602BIJ	CS	methylprednisolone	iv	1	1	1	1	1	4
193603BIJ	CS	methylprednisolone	iv	1	1	1	1	1	4
193604BIJ	CS	methylprednisolone	iv	1	1	1	1	1	4
206901ATB	Xanthine	oxtriphylline	oral	1	1	0	0	1	1
216401ACH	LTRA	pranlukast	oral	1	1	1	0	1	1
216402ASS	LTRA	pranlukast	oral	1	1	1	0	1	1
216402ASY	LTRA	pranlukast	oral	1	1	1	0	1	1
216403ACH	LTRA	pranlukast	oral	1	1	1	0	1	1
216404ATB	LTRA	pranlukast	oral	1	1	1	0	1	1
216405ASS	LTRA	pranlukast	oral	1	1	1	0	1	1
216405ATB	LTRA	pranlukast	oral	1	1	1	0	1	1
216406ASS	LTRA	pranlukast	oral	1	1	1	0	1	1
216407ASS	LTRA	pranlukast	oral	1	1	1	0	1	1
216408ATB	LTRA	pranlukast	oral	0	0	1	0	1	1
216430ASY	LTRA	pranlukast	oral	0	0	1	0	1	1
216431ASY	LTRA	pranlukast	oral	0	0	1	0	1	1
216432ASY	LTRA	pranlukast	oral	0	0	1	0	1	1
216433ASY	LTRA	pranlukast	oral	0	0	1	0	1	1
217001ATB	CS	prednisolone	oral	1	1	1	1	1	4
217003ASY	CS	prednisolone	oral	1	1	1	1	1	4
217004ASY	CS	prednisolone	oral	1	1	1	1	1	4
217030ASY	CS	prednisolone	oral	0	0	1	1	1	4
217034ASY	CS	prednisolone	oral	0	0	1	1	1	4
217035ASY	CS	prednisolone	oral	0	0	1	1	1	4
217302BIJ	CS	prednisolone	iv	1	1	1	1	1	4
218301ATB	SABA	procaterol	oral	1	1	1	0	0	0
218302ATB	SABA	procaterol	oral	1	1	1	0	0	0
218304CSI	SABA	procaterol	inhaled	1	1	1	0	30	0
218330CSI	SABA	procaterol	inhaled	0	0	1	0	30	0
225501ATB	SABA	salbutamol	oral	1	1	1	0	0	0
225502CSI	SABA	salbutamol	inhaled	1	1	1	0	0	0
225503ACR	SABA	salbutamol	oral	1	1	1	0	0	0
225503ATB	SABA	salbutamol	oral	1	1	1	0	0	0
225506CSI	SABA	salbutamol	inhaled	1	1	1	1	0	0
225507ACR	SABA	salbutamol	oral	1	1	1	0	0	0
225508CSI	SABA	salbutamol	inhaled	1	1	1	1	0	0
225530CSI	SABA	salbutamol	inhaled	0	0	1	1	0	0
225531CSI	SABA	salbutamol	inhaled	0	0	1	0	0	0
225532CSI	SABA	salbutamol	inhaled	0	0	1	1	0	0
235801ATB	SABA	terbutaline	oral	1	1	1	0	0	0
235830CLQ	SABA	terbutaline	inhaled	1	1	1	0	0	0
237001ACH	Xanthine	theophylline	oral	1	1	1	0	1	1
237001ACR	Xanthine	theophylline	oral	1	1	1	0	1	1
237002ACR	Xanthine	theophylline	oral	1	1	1	0	1	1
237003ACH	Xanthine	theophylline	oral	1	1	1	0	1	1
237003ACR	Xanthine	theophylline	oral	1	1	1	0	1	1
237003ASY	Xanthine	theophylline	oral	1	1	1	0	1	1
237003ATR	Xanthine	theophylline	oral	1	1	1	0	1	1
237005ATR	Xanthine	theophylline	oral	1	1	1	0	1	1
237030ASY	Xanthine	theophylline	oral	0	0	1	0	1	1
237031ASY	Xanthine	theophylline	oral	0	0	1	0	1	1
249701ATB	LTRA	zafirlukast	oral	1	1	1	0	1	1
264800ATB	LABA	clenbuterol	oral	0	1	1	0	1	1
334500CSI	CS & LABA	fluticasone	inhaled	1	1	1	0	30	2
334600CSI	CS & LABA	fluticasone	inhaled	1	1	1	0	30	2

334700CSI	CS & LABA	fluticasone	inhaled	1	1	1	0	30	3
374601ASY	LTRA	montelukast	oral	1	1	1	0	1	1
374601ATB	LTRA	montelukast	oral	1	1	1	0	1	1
374601ATD	LTRA	montelukast	oral	1	1	1	0	1	1
374602ATB	LTRA	montelukast	oral	1	1	1	0	1	1
374602ATD	LTRA	montelukast	oral	1	1	1	0	1	1
374603AGN	LTRA	montelukast	oral	1	1	1	0	1	1
374603ASY	LTRA	montelukast	oral	1	1	1	0	1	1
374603ATB	LTRA	montelukast	oral	1	1	1	0	1	1
374603ATD	LTRA	montelukast	oral	1	1	1	0	1	1
391800CSI	CS & LABA	budesonide	inhaled	1	1	1	0	30	1
439101ATB	Xanthine	doxofylline	oral	1	1	1	0	1	1
441700CSI	CS & LABA	budesonide	inhaled	1	1	1	0	30	1
452101CPC	LABA	tulobuterol	patch	1	1	1	0	1	1
452102CPC	LABA	tulobuterol	patch	1	1	1	0	1	1
452103CPC	LABA	tulobuterol	patch	1	1	1	0	1	1
453400CSI	CS & LABA	budesonide	inhaled	1	1	1	0	30	3
497101CSI	CS	ciclesonide	inhaled	1	1	1	0	30	1
497102CSI	CS	ciclesonide	inhaled	1	1	1	0	30	1
497130CSI	CS	ciclesonide	inhaled	0	0	1	0	30	1
497131CSI	CS	ciclesonide	inhaled	0	0	1	0	30	1
502000CSI	CS & LABA	formoterol	inhaled	1	1	1	0	30	2
503430CSI	anticholinergic	tiotropium	inhaled	0	0	1	0	30	4
506400CSI	CS & LABA	fluticasone	inhaled	1	1	1	0	30	2
506500CSI	CS & LABA	fluticasone	inhaled	1	1	1	0	30	2
506600CSI	CS & LABA	fluticasone	inhaled	1	1	1	0	30	3
525700CSI	CS & LABA	fluticasone	inhaled	1	1	1	0	30	2
525800CSI	CS & LABA	fluticasone	inhaled	1	1	1	0	30	2
526200CSI	CS & LABA	fluticasone	inhaled	1	1	1	0	30	3
531700ASY	LABA	clenbuterol	oral	0	0	1	0	1	1
531800ASY	LABA	clenbuterol	oral	0	0	1	0	1	1
531900ASY	LABA	clenbuterol	oral	0	0	1	0	1	1
532000ASY	LABA	clenbuterol	oral	0	0	1	0	1	1
532100ASY	LABA	clenbuterol	oral	0	0	1	0	1	1
532200ASY	LABA	clenbuterol	oral	0	0	1	0	1	1
532300ASY	LABA	clenbuterol	oral	0	0	1	0	1	1
542800CSI	CS & LABA	fluticasone	inhaled	0	0	1	0	30	2
542900CSI	CS & LABA	fluticasone	inhaled	0	0	1	0	30	2
543000CSI	CS & LABA	fluticasone	inhaled	0	0	1	0	30	3
543100CSI	CS & LABA	fluticasone	inhaled	0	0	1	0	30	2
543200CSI	CS & LABA	fluticasone	inhaled	0	0	1	0	30	2
543300CSI	CS & LABA	fluticasone	inhaled	0	0	1	0	30	2
543400CSI	CS & LABA	fluticasone	inhaled	0	0	1	0	30	2
543500CSI	CS & LABA	fluticasone	inhaled	0	0	1	0	30	3
543600CSI	CS & LABA	budesonide	inhaled	0	0	1	0	30	2
543800CSI	CS & LABA	budesonide	inhaled	0	0	1	0	30	2
543900CSI	CS & LABA	budesonide	inhaled	0	0	1	0	30	2
544000CSI	CS & LABA	budesonide	inhaled	0	0	1	0	30	2
544100CSI	CS & LABA	budesonide	inhaled	0	0	1	0	30	3
544200CSI	CS & LABA	beclomethasone	inhaled	0	0	1	0	30	2
544300CSI	CS & LABA	fluticasone	inhaled	0	0	1	0	14	2
544400CSI	CS & LABA	fluticasone	inhaled	0	0	1	0	14	2
544500CSI	CS & LABA	fluticasone	inhaled	0	0	1	0	14	3
636700CSI	CS & LABA	fluticasone & vilanterol	inhaled	0	1	1	0	30	2
636800CSI	CS & LABA	fluticasone & vilanterol	inhaled	0	1	1	0	30	3
640400CSI	CS & LABA	formoterol	inhaled	0	0	1	0	30	2
801100CSI	CS & LABA	formoterol	inhaled	0	0	1	0	30	2